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(54) 3-Aza-6,8-dioxabicyclo[3.2.1]octanes and analogues and combinatorial libraries containing them

(57) The present invention relates to new highly functionalized heterobicycle derivatives of following general formula (I), prepared by a process which involves only two steps by using, as starting products, commercially available, or easily prepared, α-amino ketones and α,β-dihydroxy acids or α-amino-β-hydroxy acids or α-hydroxy-β-amino acids or α,β-dithiol acids derivatives and to libraries containing compounds of formula I and to the generation of such combinatorial libraries composed of compounds of formula I, in individual synthesis, mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or automated fashion.

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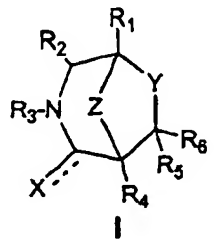
Description

Field of the Invention

[0001] The present invention refers to heterobicycle derivatives of general formula (I)



I

wherein:

R_1, is chosen in the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; RR'N-C_{1-8}alkyl, RR'N-aryl, RO-aryl, R(O)C-aryl, RO(O)C-aryl, RR'N(O)C-aryl, (P)-W-NR-aryl, (P)-W-O-aryl, (P)-W-C(O)O-aryl, (P)-W-O(O)C-aryl, (P)-W-C(O)RN-aryl, (P)-W-NR(O)C-aryl;
R_2, is chosen in the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; aminoC_{1-8}alkyl, aminoaryl, C_{1-8}alkyloxyaryl, hydroxyaryl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl,-(side chain), -(side chain)-W-(P) or
R_1 and R_2 taken together are a C_{1-4}alkyl, C_{2-4}alkenyl, cycloalkyl, benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms;
R_3, is chosen in the group consisting H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; RR'NC_{1-8}alkyl, RR'Naryl, RO-C_{1-8}alkyl, RO(O)C-C_{1-8}alkyl, R(O)C-C_{1-8}alkyl, RC(O)O-C_{1-8}alkyl, RC(O)N(R)C_{1-8}alkyl RO-aryl, RO(O)C-aryl, R(O)C-aryl RC(O)O-aryl, RC(O)N(R)aryl, -CH(amino acid side-chain)CO_2R, -CH(amino acid side-chain)C(O)NR, -CH(amino acid side-chain)-C(O)O-W-(P), -CH(amino acid side-chain)-C(O)N(R)-W-(P), CH(CO_2R)-amino acid side-chain-W-(P), CH(CONRR')-amino acid side-chain-W-(P), protecting group;
R_4 and R_5, same or different, are chosen in the group consisting H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl;
R_6 is chosen in the group consisting, H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl, heterocycle, heterocycleC_{1-8}alkyl; -C(O)R, -C(O)OR, -C(O)NRR', CH_2OR, CH_2NRR', -C(O)NH-CH(amino acid side-chain)C(O)OR, -C(O)O-W-(P),-C(O)N(R)-W-(P), -CH_2O-W-(P), -CH_2N(R)-W-(P);
R and R', same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; a protecting group, -C(O)CH-(amino acid side-chain)-NHR, -NH-CH(amino acid side-chain)COOR, -CH(amino acid side-chain)COOR;
P is resin, both soluble or bound to a solid support;
W is as linker;
X is O, S, when a is a double bond, or X is H and a is single bond,
Y and Z, same or different, are O, S, SO, SO_2, N-R, wherein R is as above defined;

the above said alkyl-, alkenyl-, alkinyl-, cycloalkyl-, aryl- and heterocycle-groups, being possibly substituted.

[0002] The application refers also to a process for the preparation of the above said compounds, to libraries containing them and to the generation of such combinatorial libraries composed of compounds of formula I, in mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or automated fashion. Compounds of formula I and their libraries are useful to discover new leads for therapeutical applications.

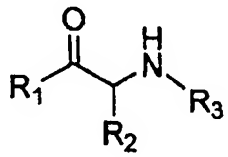
State of the art

[0003] The process of discovering new therapeutically active compounds involves the screening of a large number of compounds, in order to develop a structure-activity relationships and select the structures which could represent a new lead for the biological target. Fast methods are necessary to prepare a large collection of compounds to submit to the screening and this, in recent years, can be achieved by preparation of combinatorial chemical libraries of well

designed chemical compounds by using immobilization techniques on soluble or insolubl resins. H terocycles compounds, b aring diff rent substituents, and functionalised with reactive groups suitable for anchoring on resins, are very us ful for this new typ of synthetic strategy (for example see US 5,925,527). Another important point for a well designed chemical library is the complete control f the configuration of the sterogenic cent rs and the possibility to have enantiopure compounds. All these above mentioned features can be incorporated in compounds of g n ral formula (I) which can b obtained with only two reaction steps starting from easily prepared precursors, available also as pure enantiomers. This n w typ of compounds, having a rigid bicyclic structure, can be functionalised in several positions and allows the easy anchoring on resin support, thus representing a new scaffold for the generation of combinatorial libraries. Thus compounds of general formula (I) can be used for the discover of new leads for therapeutical applications.

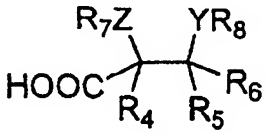
[0004] Compounds of general formula (I) having R_1 = H, Y and Z = O, have been already prepared as it is described by us in *JOC* 1999, *64*, 7347 by a process involving various steps starting from a suitable α-amino alcohol which is coupled with a tartaric acid derivative. The prepared intermediate required an oxidation of the primary alcohol function to the corresponding aldehyde and a subsequent transacetalization to arrive to compounds I having R_1 = H and X,Y and Z = O. However, it can be seen that the above described process involves many steps which can have a negative effect on the final yields of the desired compounds and the application cannot be extended to compound having R_1 different from H, and Z and Y different from O. Moreover this above described process is limited because, involving also an oxidative step, is compatible only with the functions resistant to the oxidative conditions and requires the protection of the all function sensitive to oxidation.

[0005] Therefore the application refers to a new straightforward process which, in only two steps, can produce compounds I, where R_1 is different from H, by starting from α-aminoketone II



II

and acid derivative III,



III

commercially available or easily prepared by reported procedures. Moreover, this procedure, allowing the immobilization of each the precursors II or III to a soluble or insoluble resin support, is suitable for the synthesis of combinatorial chemical libraries (see for examples *J Med Chem* **1999**, *42*, 3743; US 5,958,792, US 5,302,589) either as separate synthesis, in mixture synthesis, split and recombine synthesis, parallel synthesis with manual or automated fashion.

Detailed description of the invention

[0006] The present invention allows to overcome the above said problems thanks to the compounds of formula (I) as above defined useful either as individual compounds or for generation of combinatorial chemical libraries either in mixture synthesis or parallel synthesis with manual or automated fashion.

[0007] Moreover the invention refers to a new an advantageous process for the preparation of the above defined compounds of formula (I) and their use for discovering new leads for therapeutical applications.

[0008] According to the present invention in the compounds of formula (I) as above defined:

Resin (P) means any polymeric material either soluble in the solvents commonly used in organic synthesis or

bound to the solid support;
Solid support is any solid material (at room temperature) to which starting resin materials (reactive groups) may be bound;
W is any molecule which can be used as linker to bound the resin P to the reagents and the products of formula (I);
Protecting group means any group capable of preventing the atom to which it is attached from participating in an undesired reaction or bonding, as commonly used in synthesis reactions.
Amino acid side-chain means the side chain moieties of the natural occurring L or D amino acids or the non naturally occurring amino acids;

[0009] More preferably the resin is a polymeric material derivatised with a reactive group such as, for example, a $-NH_2$ group or other electron donating group such as an hydroxyl group.

[0010] Preferred solid support materials comprise polymeric compounds such as polyethylene and polystyrene compounds and related inert polymeric compounds. The substrate may be in any shape including sheets, the inside of a cylindrical vessel, or pins but are preferably in the form of spherical beads less than 1.0 cm in diameter more preferably less than 1.0 mm in diameter. A "substrate" or solid support is a conventional solid support material used in peptide synthesis. Non-limiting examples of such substrates or supports include a variety of support resins and connectors to the support resins such as those which are photocleavable, DKP-forming linkers (DKP is diketopiperazine; see, e.g., WO90/09395 incorporated herein by reference), TFA cleavable, HF cleavable, fluoride ion cleavable, reductively cleavable and base-labile linkers.

[0011] A solid support resin comprises a plurality of solid support particles which can be split into portions for separate reactions and recombined as desired.

[0012] Preferred protecting groups are those which prevent reaction or bonding of oxygen, nitrogen, carboxylic acids, thiols, alcohols, amines and the like. Such groups and their preparation and introduction are conventional in the art and include, for example, for the reactive function OH: benzyl, *tert*-butyl; acetals, esters, trialkylsilylethers; for COOH group: methyl, tert-butyl, benzyl, allyl esters; for the NH group: t-Boc, Fmoc, CBz, Bn, Bz.

[0013] Amino acid side-chain means the different amino acid side-chain moieties attached to an "amino acid". The term "amino acid" includes any one of the twenty L or D natural α-amino acids having as " side chain":, -H of glycine; $-CH_3$ of alanine; $-CH(CH_3)_2$ of valine; $-CH_2CH(CH_3)_2$ of leucine; $-CH(CH_3)CH_2CH_3$ of isoleucine; $-CH_2OH$ of serine; $-CH(OH)CH_3$ of threonine; $-CH_2SH$ of cysteine; $-CH_2CH_2SCH_3$ of methionine; $-CH_2$-(phenyl) of phenylalanine; $-CH_2$-(phenyl)-OH of tyrosine; $-CH_2$-(indole group) of tryptophan; $-CH_2COOH$ of aspartic acid; $-CH_2C(O)(NH_2)$ of asparagine; $-CH_2CH_2COOH$ of glutamic acid; $-CH_2CH_2C(O)NH_2$ of glutamine; $-CH_2CH_2CH_2-N(H)C(NH_2)NH$ of arginine; $-CH_2$-(imidazole) group of histidine; and $-CH_2(CH_2)_3NH_2$ of lysine, comprising the same amino acid side-chain moieties bearing suitable protecting groups (Pg). In addition, the term "amino acid" include also non naturally occurring amino acids, like norleucine (Nle), norvaline (NVa), β-alanine, L or D α-phenyl glycine and others well known in the peptide art.

[0014] In the compounds of formula (I), as above defined, groups C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkinyl represent linear or branched alkyl radicals as for example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, thylene, propene, butene, isobutene, acetylene, propine, butine etc

[0015] The term cycloalkyl represents: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane.

[0016] The term aryl specifies phenyl, biphenyl and naphtyl groups substituted with one or more, and preferably one or two moieties chosen from the groups consisting of halogen, cyano, nitro, C_{1-6} alkyl. The term heterocycle represents in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, pyperidine.

[0017] The term halogen represent fluorine, chlorine, bromine, iodine.

[0018] The terms "library", "combinatorial library", "resin-derived library" and the like are used interchangeably throughout the description to mean a series of separate individual components or mixture of the compounds I, synthesized in solution or on a solid support from one or more solid phase bound resin starting materials. and their pharmaceutically acceptable salts or esters.

[0019] The synthetic process according to the invention involves only two steps and moreover uses, as starting compounds, an α-aminoketone and a carboxylic acid derivative bearing two vicinal nucleophilic groups like OH, SH, or NHR, preferably belonging to the classes of α,β-dihydroxy acid or α-amino-β-hydroxy acid or α-hydroxy-β-amino acid or α,β-dithiol acid derivatives.

[0020] In particular, the process according to the present invention allows the preparation of the compounds of formula (I) wherein:

a = double bond, and X = O or a = single bond and X = H
Y and Z, same or different are O, S, NR wherein R is above described
R_1 = methyl, ethyl, propyl, isopropyl, t-butyl, benzyl, phenyl, 4-hydrophenyl, 4-methoxy-phenyl, 4-carboxy-phenyl,

4-nitro-phenyl, 4-amino-ph nyl, 4-halog nphenyl, 4-trifluorom thylphenyl, 2-hydroph nyl, 2-methoxy-phenyl, 2-carboxyph nyl, 2-nitro-ph nyl, 2-amino-ph nyl, 2-halogen-phenyl, 2-trifluoromethylphenyl C_{1-8}alkylOC(O)phenyl, hydroxy-C_{1-8}alkylph nyl, methoxy-C_{1-8}alkylphenyl, RR'NC(O)-phenyl, RR'N-C_{1-8}alkylphenyl, biph nyl, naphtyl, tetrahydronapthyl, decahydr naphtyl, cycloalkyl, heterocycl , (P)-W-NR-phenyl, (P)-W-O-phenyl, (P)-W-C(O)O-phenyl, (P)-W-O(O)C-ph nyl, (P)-W-C(O)RN-phenyl, (P)-W-NR(O)C-ph nyl, wherein (P), W, R and R' are defined as above;

R_2, which can b bound with R_1 through a C_1-C_5alkyl chain, is chosen in the group consisting of H, methyl, thyl, propyl, isopropyl, t-butyl, phenyl, 4-hydrophenyl, 4-methoxy-phenyl, 4-carboxy-phenyl, 4-amino-phenyl, benzyl, amino acid side chain-; (P)-W-amino acid side-chain;

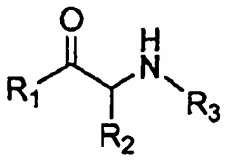
R_3, H, methyl, ethyl, propyl, isopropyl, t-butyl, phenyl, benzyl, cycloalkyl, aryl, arylC_{1-8}alkyl; heterocycle, heterocycleC_{1-8}alkyl-CH(amino acid side-chain)CO_2R, CH(amino acid side-chain)C(O)NR, -CH(amino acid side-chain)-C(O)O-W-(P),-CH(amino acid side-chain)-C(O)N(R)-W-(P), CH(CO_2R)-amino acid side-chain-W-(P), CH (CONRR')- amino acid side-chain-W-(P), Pg, wherein (P), (amino acid side-chain), W, R and R' are defined as above;

R_4, R_5, same or different, are chosen in the group consisting H, methyl, ethyl, propyl, isopropyl, phenyl, benzyl, heterocycle

R_6 is chosen in the group consisting, H, methyl, ethyl, propyl, isopropyl, t-butyl, phenyl, benzyl, cycloalkyl, aryl, benzyl, heterocycle, heterocycleC_{1-8}alkyl; COOH, COOR, C(O)R, CONHR CONRR', CH_2OH, CH_2OR CH_2NHR, CH_2NRR', -C(O)NH-CH(amino acid side-chain)C(O)OR, -C(O)O-W-(P), -C(O)N(R)-W-(P), -CH_2O-W-(P), -CH_2N(R)-W-(P), wherein R and R' same or different and the terms "(amino acid side-chain)", "(P)", and "W" are as above defined

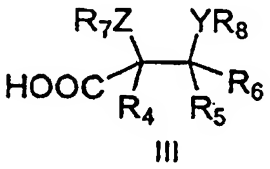
[0021] Among the pharmaceutically acceptable esters and salts according to the present invention the following can be mentioned: hydrochloride, sulfate, citrate, formiate, phosphate.

[0022] According to the invention the above defined compounds of formula (I) can be prepared starting from compounds of general formula II



II

wherein R_1, R_2, R_3, are as above defined
and III



III

wherein R_4, R_5, R_6, Y and Z are as above defined,
and R_7 R_8 represent H or suitable protecting groups, (Pg) which can be same or different, cyclic or acyclic, and which can be cleaved in acidic conditions.

[0023] The α-amino ketones II are commercially available or can be prepared as shown in the scheme 2, for example starting from an α-halogen-ketone V and a primary amine VI according to known procedures (see for example *Tetrahedron Letters* 1987, *28*, 1287 and references cited therein)

[0024] The acid derivatives III are commercial available o can be prepared according know procedures.

[0025] As it can be seen from the Scheme 1 the preparation of the compounds (I) according to the invention involves, in the Step 1, the reaction of the α-amino ketone II with the acid derivative III to give the amide derivative IV in the

presence of a coupling reagent. Because Step I involves the formation of an amide bond , all the reag nts commonly used for the peptide synth sis can b appli d to this step. Pr f rably the reaction is performed in an aprotic polar solvent, preferably CH_2Cl_2 or DMF, at a temperature compris d b tween 0°C - 100°C, preferably at 25°C, for a time comprised between 1 and 24 hours, preferably in th presence of a coupling ag nt and activator of the carboxy group, as PyBrOP, PyBOP, HATU, HOBt, HBTU, TBTU, DCC, DIC, EDC etc. and a tertiary bas as NEt_3, DIPEA, NMM.

[0026] The intermediate amide IV is then cyclized into th final compound I in the Step 2, by action of an acid, which, allows the ketalization of the functions Z and Y with the carbonyl group by als removing th protecting groups Pg, when present. Also for this step the reaction conditions (temperature and time) and the type of acid and solvent are important.

[0027] The best results were obtained using a stechiometric or preferably catalytic amount of a strong acid, preferably sulphuric acid adsorbed on silica gel, p-toluen sulphonic acid, trifluoroacetic acid, trifluorometansulphonic acid and performing the reaction at a temperature comprised between 0°C - 150°C, preferably at refluxing-solvent temperature, in an organic apolar solvent (for example methylene chloride, chloroform, benzene or toluene) for a time comprised between 15 min and 24 hours, preferably 30 min -2 hours, preferably with the simultaneous removal of a portion of the solvent and eventually in the presence of molecular sieves. In these condition the final product I is obtained having X=O and *a* double bond. The subsequent reaction on the amide bond either with usual reducing agents, for example $LiAlH_4$, BH_3.THF, $BH_3.Me_2S$ and like, produce compounds I wherein X=H and a is single bond, or by the use of sulphurating agents, like the Lawesson reagent, produce compounds I wherein X=S and *a* is double bond.

[0028] Owing to the importance to produce combinatorial chemical libraries, the above reported procedure can be modified by using one of the two components II and III of the Step 1 bound to a resin through a suitable linker. In this case, the formed compound IV is also bound to a resin, and the following step 2 can be performed either maintaining the final product I bound to the resin or with a simultaneous cleavage from the resin. Because the starting α-amino ketone II can be easily prepared from an α-halogen ketone V and a primary amine VI (as reported in the Scheme 2), this can increase the molecular diversity of compounds II, by starting from of one of the two components V or VI, already immobilized on the resin-support.

[0029] Specific compounds I prepared according to the process of the invention are reported in the following table:

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
1.	O	O	O	Ph	H	$PhCH_2$	H	H	COOH
2.	O	O	O	4-HO-Ph	H	$PhCH_2$	H	H	COOH
3.	O	O	O	4-O_2N-Ph	H	$PhCH_2$	H	H	COOH
4.	O	O	O	4-H_2N-Ph	H	$PhCH_2$	H	H	COOH
5.	O	O	O	4-MeO(O)C-Ph	H	$PhCH_2$	H	H	COOH
6.	O	O	O	4-Me-Ph	H	$PhCH_2$	H	H	COOH
7.	O	O	O	4-MeO-Ph	H	$PhCH_2$	H	H	COOH
8.	O	O	O	4-Cl-Ph	H	$PhCH_2$	H	H	COOH
9.	O	O	O	4-Br-Ph	H	$PhCH_2$	H	H	COOH
10.	O	O	O	2-HO-Ph	H	$PhCH_2$	H	H	COOH
11.	O	O	O	2-O_2N-Ph	H	$PhCH_2$	H	H	COOH
12.	O	O	O	2-H_2N-Ph	H	$PhCH_2$	H	H	COOH
13.	O	O	O	2-MeO(O)C-Ph	H	$PhCH_2$	H	H	COOH
14.	O	O	O	2-Me-Ph	H	$PhCH_2$	H	H	COOH
15.	O	O	O	2-MeO-Ph	H	$PhCH_2$	H	H	COOH
16.	O	O	O	2-Cl-Ph	H	$PhCH_2$	H	H	COOH
17.	O	O	O	2-Br-Ph	H	$PhCH_2$	H	H	COOH
18.	O	O	O	2-Nafthyl	H	$PhCH_2$	H	H	COOH
19.	O	O	O	2-thienyl	H	$PhCH_2$	H	H	COOH
20.	O	O	O	4-biphenyl	H	$PhCH_2$	H	H	COOH
21.	O	O	O	Ph	H	Me	H	H	COOH
22.	O	O	O	Ph	H	$CH_3(CH_2)_2$	H	H	COOH
23.	O	O	O	Ph	H	cyclohexyl	H	H	COOH
24.	O	O	O	Ph	H	allyl	H	H	COOH
25.	O	O	O	Ph	H	Ph	H	H	COOH
26.	O	O	O	Ph	H	4-HO-Ph	H	H	COOH

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
27.	O	O	O	Ph	H	4-O_2N-Ph	H	H	COOH
28.	O	O	O	Ph	H	4-M O_2C-Ph	H	H	COOH
29.	O	O	O	Ph	H	4-Me-Ph	H	H	COOH
30.	O	O	O	Ph	H	4-MeO-Ph	H	H	COOH
31.	O	O	O	Ph	H	4-Cl-Ph	H	H	COOH
32.	O	O	O	Ph	H	4-Br-Ph	H	H	COOH
33.	O	O	O	Ph	H	2-HO-Ph	H	H	COOH
34.	O	O	O	Ph	H	2-O_2N-Ph	H	H	COOH
35.	O	O	O	Ph	H	2-MeO_2C-Ph	H	H	COOH
36.	O	O	O	Ph	H	2-Me-Ph	H	H	COOH
37.	O	O	O	Ph	H	2-MeO-Ph	H	H	COOH
38.	O	O	O	Ph	H	2-Cl-Ph	H	H	COOH
39.	O	O	O	Ph	H	2-Br-Ph	H	H	COOH
40.	O	O	O	Ph	H	2-Nafthyl	H	H	COOH
41.	O	O	O	Ph	H	2-thienyl	H	H	COOH
42.	O	O	O	Ph	H	4-biphenyl	H	H	COOH
43.	O	O	O	Ph	H	4-MeO_2C-PhCH_2	H	H	COOH
44.	O	O	O	Ph	H	4-Me-PhCH_2	H	H	COOH
45.	O	O	O	Ph	H	4-MeOPhCH_2	H	H	COOH
46.	O	O	O	Ph	H	4-Cl-PhCH_2	H	H	COOH
47.	O	O	O	Ph	H	4-Br-PhCH_2	H	H	COOH
48.	O	O	O	Ph	H	2-HO-PhCH_2	H	H	COOH
49.	O	O	O	Ph	H	2-O_2N-PhCH_2	H	H	COOH
50.	O	O	O	Ph	H	2-MeO_2C-PhCH_2	H	H	COOH
51.	O	O	O	Ph	H	2-Me-PhCH_2	H	H	COOH
52.	O	O	O	Ph	H	2-MeO-PhCH_2	H	H	COOH
53.	O	O	O	Ph	H	2-Cl-PhCH_2	H	H	COOH
54.	O	O	O	Ph	H	2-Br-PhCH_2	H	H	COOH
55.	O	O	O	4-HO-Ph	H	4-HO-Ph CH_2	H	H	COOH
56.	O	O	O	4-HO-Ph	H	4-O_2N-PhCH_2	H	H	COOH
57.	O	O	O	4-HO-Ph	H	4-MeO_2C-PhCH_2	H	H	COOH
58.	O	O	O	4-HO-Ph	H	4-Me-PhCH_2	H	H	COOH
59.	O	O	O	4-HO-Ph	H	4-MeOPhCH_2	H	H	COOH
60.	O	O	O	4-HO-Ph	H	4-Cl-PhCH_2	H	H	COOH
61.	O	O	O	4-HO-Ph	H	4-Br-PhCH_2	H	H	COOH
62.	O	O	O	4-HO-Ph	H	2-HO-PhCH_2	H	H	COOH
63.	O	O	O	4-HO-Ph	H	2-O_2N-PhCH_2	H	H	COOH
64.	O	O	O	4-HO-Ph	H	2-MeO_2C-PhCH_2	H	H	COOH
65.	O	O	O	4-HO-Ph	H	2-Me-PhCH_2	H	H	COOH
66.	O	O	O	4-HO-Ph	H	2-MeO-PhCH_2	H	H	COOH
67.	O	O	O	4-HO-Ph	H	2-Cl-PhCH_2	H	H	COOH
68.	O	O	O	4-HO-Ph	H	2-Br-PhCH_2	H	H	COOH
69.	O	O	O	4-HO-Ph	H	Me	H	H	COOH
70.	O	O	O	4-HO-Ph	H	$CH_3(CH_2)_2$	H	H	COOH
71.	O	O	O	4-HO-Ph	H	cyclohexyl	H	H	COOH
72.	O	O	O	4-HO-Ph	H	allyl	H	H	COOH
73.	O	O	O	Ph	H	HO_2C-CH_2	H	H	COOH
74.	O	O	O	Ph	H	Bn(HO_2C)CH	H	H	COOH
75.	O	O	O	Ph	H	$HOCH_2$(HO_2C)CH	H	H	COOH

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
76.	O	O	O	Ph	H	$CH_3(HO)CH(HO_2C)CH$	H	H	COOH
77.	O	O	O	Ph	H	$MeS(CH_2)_2(HO_2C)CH$	H	H	COOH
78.	O	O	O	Ph	H	$H_2N(CH_2)_3(HO_2C)CH$	H	H	COOH
79.	O	O	O	Ph	H	$HO_2CCH_2(HO_2C)CH$	H	H	COOH
80.	O	O	O	Ph	H	imidazole-$CH_2(HO_2C)CH$	H	H	COOH
81.	O	O	O	Ph	H	indole-$CH_2(HO_2C)CH$	H	H	COOH
82.	O	O	O	4-HO-Ph	H	HO_2C-CH_2	H	H	COOH
83.	O	O	O	4-HO-Ph	H	$Me(HO_2C)CH$	H	H	COOH
84.	O	O	O	4-HO-Ph	H	$(CH_3)_2CH(HO_2C)CH$	H	H	COOH
85.	O	O	O	4-HO-Ph	H	$Bn(HO_2C)CH$	H	H	COOH
86.	O	O	O	4-HO-Ph	H	$HOCH_2(HO_2C)CH$	H	H	COOH
87.	O	O	O	4-HO-Ph	H	$CH_3(HO)CH(HO_2C)CH$	H	H	COOH
88.	O	O	O	4-HO-Ph	H	$MeS(CH_2)_2(HO_2C)CH$	H	H	COOH
89.	O	O	O	4-HO-Ph	H	$H_2N(CH_2)_3(HO_2C)CH$	H	H	COOH
90.	O	O	O	4-HO-Ph	H	$HO_2CCH_2(HO_2C)CH$	H	H	COOH
91.	O	O	O	4-HO-Ph	H	imidazole-$CH_2(HO_2C)CH$	H	H	COOH
92.	O	O	O	4-HO-Ph	H	indole-$CH_2(HO_2C)CH$	H	H	COOH
93.	O	O	O	Ph	Me	$PhCH_2$	H	H	COOH
94.	O	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	COOH
95.	O	O	O	Ph	Bn	$PhCH_2$	H	H	COOH
96.	O	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	COOH
97.	O	O	O	Ph	Me	HO_2C-CH_2	H	H	COOH
98.	O	O	O	4-HO-Ph	Me	HO_2C-CH_2	H	H	COOH
99.	O	O	O	Ph	Bn	HO_2C-CH_2	H	H	COOH
100.	O	O	O	4-HO-Ph	Bn	HO_2C-CH_2	H	H	COOH
101.	O	O	O	Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
102.	O	O	O	4-HO-Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
103.	O	HN	O	Ph	H	$PhCH_2$	H	H	CH_3
104.	O	HN	O	Ph	Me	$PhCH_2$	H	H	CH_3
105.	O	HN	O	Ph	Bn	$PhCH_2$	H	H	CH_3
106.	O	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	CH_3
107.	O	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	CH_3
108.	O	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	CH_3
109.	O	HN	O	Ph	H	Ph	H	H	CH_3
110.	O	HN	O	Ph	Me	Ph	H	H	CH_3
111.	O	HN	O	Ph	Bn	Ph	H	H	CH_3
112.	O	HN	O	4-OH-Ph	H	Ph	H	H	CH_3
113.	O	HN	O	4-OH-Ph	Me	Ph	H	H	CH_3
114.	O	HN	O	4-OH-Ph	Bn	Ph	H	H	CH_3
115.	O	HN	O	Ph	H	CH_3-Ph	H	H	CH_3
116.	O	HN	O	Ph	Me	CH_3-Ph	H	H	CH_3
117.	O	HN	O	Ph	Bn	CH_3-Ph	H	H	CH_3
118.	O	HN	O	4-OH-Ph	H	CH_3-Ph	H	H	CH_3
119.	O	HN	O	4-OH-Ph	Me	CH_3-Ph	H	H	CH_3
120.	O	HN	O	4-OH-Ph	Bn	CH_3-Ph	H	H	CH_3
121.	O	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
122.	O	HN	O	Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
123.	O	HN	O	Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
124.	O	HN	O	4-OH-Ph	H	4-MeO-$PhCH_2$	H	H	CH_3

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
125.	O	HN	O	4-OH-Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
126.	O	HN	O	4-OH-Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
127.	O	HN	O	Ph	H	CH_3-$PhCH_2$	H	H	CH_3
128.	O	HN	O	Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
129.	O	HN	O	Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
130.	O	HN	O	4-OH-Ph	H	CH_3-$PhCH_2$	H	H	CH_3
131.	O	HN	O	4-OH-Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
132.	O	HN	O	4-OH-Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
133.	O	HN	O	Ph	H	Me	H	H	CH_3
134.	O	HN	O	Ph	H	$CH_3(CH_2)_2$	H	H	CH_3
135.	O	HN	O	Ph	H	cyclohexyl	H	H	CH_3
136.	O	HN	O	Ph	H	allyl	H	H	CH_3
137.	O	HN	O	4-OH-Ph	H	Me	H	H	CH_3
138.	O	HN	O	4-OH-Ph	H	$CH_3(CH_2)_2$	H	H	CH_3
139.	O	HN	O	4-OH-Ph	H	cyclohexyl	H	H	CH_3
140.	O	HN	O	4-OH-Ph	H	allyl	H	H	CH_3
141.	O	HN	O	Ph	H	HO_2C-CH_2	H	H	CH_3
142.	O	HN	O	Ph	Me	HO_2C-CH_2	H	H	CH_3
143.	O	HN	O	Ph	Bn	HO_2C-CH_2	H	H	CH_3
144.	O	HN	O	4-OH-Ph	H	HO_2C-CH_2	H	H	CH_3
145.	O	HN	O	4-OH-Ph	Me	HO_2C-CH_2	H	H	CH_3
146.	O	HN	O	4-OH-Ph	Bn	HO_2C-CH_2	H	H	CH_3
147.	O	HN	O	Ph	H	Bn(HO_2C)CH	H	H	CH_3
148.	O	HN	O	Ph	Me	Bn(HO_2C)CH	H	H	CH_3
149.	O	HN	O	Ph	Bn	Bn(HO_2C)CH	H	H	CH_3
150.	O	HN	O	4-OH-Ph	H	Bn(HO_2C)CH	H	H	CH_3
151.	O	HN	O	4-OH-Ph	Me	Bn(HO_2C)CH	H	H	CH_3
152.	O	HN	O	4-OH-Ph	Bn	Bn(HO_2C)CH	H	H	CH_3
153.	H	O	O	Ph	H	$PhCH_2$	H	H	COOH
154.	H	O	O	Ph	Me	$PhCH_2$	H	H	COOH
155.	H	O	O	Ph	Bn	$PhCH_2$	H	H	COOH
156.	H	O	O	4-HO-Ph	H	$PhCH_2$	H	H	COOH
157.	H	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	COOH
158.	H	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	COOH
159.	H	O	O	Ph	H	HO_2C-CH_2	H	H	COOH
160.	H	O	O	Ph	Me	HO_2C-CH_2	H	H	COOH
161.	H	O	O	Ph	Bn	HO_2C-CH_2	H	H	COOH
162.	H	O	O	4-HO-Ph	H	HO_2C-CH_2	H	H	COOH
163.	H	O	O	4-HO-Ph	Me	HO_2C-CH_2	H	H	COOH
164.	H	O	O	4-HO-Ph	Bn	HO_2C-CH_2	H	H	COOH
165.	H	O	O	Ph	H	Bn(HO_2C)CH	H	H	COOH
166.	H	O	O	Ph	Me	Bn(HO_2C)CH	H	H	COOH
167.	H	O	O	Ph	Bn	Bn(HO_2C)CH	H	H	COOH
168.	H	O	O	4-HO-Ph	H	Bn(HO_2C)CH	H	H	COOH
169.	H	O	O	4-HO-Ph	Me	Bn(HO_2C)CH	H	H	COOH
170.	H	O	O	4-HO-Ph	Bn	Bn(HO_2C)CH	H	H	COOH
171.	H	HN	O	Ph	H	$PhCH_2$	H	H	CH_3
172.	H	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
173.	H	HN	O	Ph	Me	$PhCH_2$	H	H	CH_3

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
174.	H	HN	O	Ph	Bn	$PhCH_2$	H	H	CH_3
175.	H	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	CH_3
176.	H	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	CH_3
177.	H	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	CH_3
178.	H	HN	O	Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
179.	H	HN	O	Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
180.	H	HN	O	Ph	Bn	$HO_2C\text{-}CH_2$	H	H	CH_3
181.	H	HN	O	4-OH-Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
182.	H	HN	O	4-OH-Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
183.	H	HN	O	4-OH-Ph	Bn	$HO_2C\text{-}CH_2$	H	H	CH_3
184.	H	HN	O	Ph	H	$Bn(HO_2C)CH$	H	H	CH_3
185.	H	HN	O	Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
186.	H	HN	O	Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
187.	H	HN	O	4-OH-Ph	H	$Bn(HO_2C)CH$	H	H	CH_3
188.	H	HN	O	4-OH-Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
189.	H	HN	O	4-OH-Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
190.	H	HN	O	Ph	H	Ph	H	H	CH_3
191.	H	HN	O	Ph	Me	Ph	H	H	CH_3
192.	H	HN	O	Ph	Bn	Ph	H	H	CH_3
193.	H	HN	O	4-OH-Ph	H	Ph	H	H	CH_3
194.	H	HN	O	4-OH-Ph	Me	Ph	H	H	CH_3
195.	H	HN	O	4-OH-Ph	Bn	Ph	H	H	CH_3
196.	H	HN	O	Ph	H	CH_3-Ph	H	H	CH_3
197.	H	HN	O	Ph	Me	CH_3-Ph	H	H	CH_3
198.	H	HN	O	Ph	Bn	CH_3-Ph	H	H	CH_3
199.	H	HN	O	4-OH-Ph	H	CH_3-Ph	H	H	CH_3
200.	H	HN	O	4-OH-Ph	Me	CH_3-Ph	H	H	CH_3
201.	H	HN	O	4-OH-Ph	Bn	CH_3-Ph	H	H	CH_3
202.	H	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
203.	H	HN	O	Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
204.	H	HN	O	Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
205.	H	HN	O	4-OH-Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
206.	H	HN	O	4-OH-Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
207.	H	HN	O	4-OH-Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
208.	H	HN	O	Ph	H	CH_3-$PhCH_2$	H	H	CH_3
209.	H	HN	O	Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
210.	H	HN	O	Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
211.	H	HN	O	4-OH-Ph	H	CH_3-$PhCH_2$	H	H	CH_3
212.	H	HN	O	4-OH-Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
213.	H	HN	O	4-OH-Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
214.	H	O	O	Ph	H	$PhCH_2$	H	H	CH_2OH
215.	H	O	O	Ph	H	4-MeO$PhCH_2$	H	H	CH_2OH
216.	H	O	O	Ph	Me	$PhCH_2$	H	H	CH_2OH
217.	H	O	O	Ph	Bn	$PhCH_2$	H	H	CH_2OH
218.	H	O	O	4-HO-Ph	H	$PhCH_2$	H	H	CH_2OH
219.	H	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	CH_2OH
220.	H	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	CH_2OH
221.	H	O	O	Ph	H	$HOCH_2$	H	H	CH_2OH
222.	H	O	O	Ph	Me	$HOCH_2$	H	H	CH_2OH

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
223.	H	O	O	Ph	Bn	$HOCH_2$	H	H	CH_2OH
224.	H	O	O	4-HO-Ph	H	$HOCH_2$	H	H	CH_2OH
225.	H	O	O	4-HO-Ph	Me	$HOCH_2$	H	H	CH_2OH
226.	H	O	O	4-HO-Ph	Bn	$HOCH_2$	H	H	CH_2OH
227.	H	O	O	Ph	H	$Bn(HOH_2C)CH$	H	H	CH_2OH
228.	H	O	O	Ph	Me	$Bn(HOH_2C)CH$	H	H	CH_2OH
229.	H	O	O	Ph	Bn	$Bn(HOH_2C)CH$	H	H	CH_2OH
230.	H	O	O	4-HO-Ph	H	$Bn(HOH_2C)CH$	H	H	CH_2OH
231.	H	O	O	4-HO-Ph	Me	$Bn(HOH_2C)CH$	H	H	CH_2OH
232.	H	O	O	4-HO-Ph	Bn	$Bn(HOH_2C)CH$	H	H	CH_2OH
233.	H	HN	O	Ph	H	$PhCH_2$	H	H	H
234.	H	HN	O	Ph	H	$4\text{-MeO-}PhCH_2$	H	H	H
235.	H	HN	O	Ph	Me	$PhCH_2$	H	H	H
236.	H	HN	O	Ph	Bn	$PhCH_2$	H	H	H
237.	H	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	H
238.	H	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	H
239.	H	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	H
240.	H	HN	O	Ph	H	$HOCH_2$	H	H	H
241.	H	HN	O	Ph	Me	$HOCH_2$	H	H	H
242.	H	HN	O	Ph	Bn	$HOCH_2$	H	H	H
243.	H	HN	O	4-OH-Ph	H	$HOCH_2$	H	H	H
244.	H	HN	O	4-OH-Ph	Me	$HOCH_2$	H	H	H
245.	H	HN	O	4-OH-Ph	Bn	$HOCH_2$	H	H	H
246.	H	HN	O	Ph	H	$Bn(HOH_2C)CH$	H	H	H
247.	H	HN	O	Ph	Me	$Bn(HOH_2C)CH$	H	H	H
248.	H	HN	O	Ph	Bn	$Bn(HOH_2C)CH$	H	H	H
249.	H	HN	O	4-OH-Ph	H	$Bn(HOH_2C)CH$	H	H	H
250.	H	HN	O	4-OH-Ph	Me	$Bn(HOH_2C)CH$	H	H	H
251.	H	HN	S	Ph	H	$PhCH_2$	H	H	H
252.	H	HN	S	Ph	H	$4\text{-MeO-}PhCH_2$	H	H	H
253.	H	HN	S	Ph	Me	$PhCH_2$	H	H	H
254.	H	HN	S	Ph	Bn	$PhCH_2$	H	H	H
255.	H	HN	S	4-OH-Ph	H	$PhCH_2$	H	H	H
256.	H	HN	S	4-OH-Ph	Me	$PhCH_2$	H	H	H
257.	H	HN	S	4-OH-Ph	Bn	$PhCH_2$	H	H	H
258.	H	HN	S	Ph	H	$HOCH_2$	H	H	H
259.	H	HN	S	Ph	Me	$HOCH_2$	H	H	H
260.	H	HN	S	Ph	Bn	$HOCH_2$	H	H	H
261.	H	HN	S	4-OH-Ph	H	$HOCH_2$	H	H	H
262.	H	HN	S	4-OH-Ph	Me	$HOCH_2$	H	H	H
263.	H	HN	S	4-OH-Ph	Bn	$HOCH_2$	H	H	H
264.	H	HN	S	Ph	H	$Bn(HOH_2C)CH$	H	H	H
265.	H	HN	S	Ph	Me	$Bn(HOH_2C)CH$	H	H	H
266.	H	HN	S	Ph	Bn	$Bn(HOH_2C)CH$	H	H	H
267.	H	HN	S	4-OH-Ph	H	$Bn(HOH_2C)CH$	H	H	H
268.	H	HN	S	4-OH-Ph	Me	$Bn(HOH_2C)CH$	H	H	H

[0030] The invention will be better understood in the light of the following Examples.

EXAMPLE 1

Preparation of *N*-benzyl-*N*'-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2]

[0031] To a solution of II (wher in R_1 = Ph, R_2 = H, R_3 = $PhCH_2$) (1.2 g, 5.33 mmol) in anhydrous CH_2Cl_2 (10 ml) (CH_2Cl_2 was filtered through a short pad of anhydrous Na_2CO_3 just before being used) were added, under a nitrogen atmosphere, III (wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (1.088 g, 5.33 mmol), PyBrOP (2.49 g, 5.33 mmol), and DIPEA (2.73 mL, 15.99 mmol). The mixture was stirred at room temperature for 2 h, and then the solvent was removed to give an oil that was dissolved in EtOAc. This solution was washed with aqueous 5% $KHSO_4$, 5% $NaHCO_3$, and brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product obtained was purified by chromatography (EtOAc-petroleum ether, 1:3, Rf 0.32), yielding IV (wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (1.645 g, 75%) as a colorless oil:
^{1}H NMR ($CDCl_3$): 7.90-7.85 (m, 2H), 7.61-7.22 (m, 8H), 5.39 (d, J = 5.1 Hz, 1H), 5.11 (d, J = 5.1Hz, 1 H), 4.88-4.10 (m, 4H), 3.80 (s, 3 H), 1.49 (s, 3 H), 1.31 (s, 3 H).

EXAMPLE 2

Preparation of Methyl (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate [compound I wherein R_1 = Ph, R_2 = H, R_3=$PhCH_2$, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O]

[0032] A solution of IV (prepared according the example 1, wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (1.645 g, 4.00 mmol) in toluene (40 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (30% w/w, 700 mg) in toluene (60 mL). The mixture was allowed to react for 15 min, and afterward, one-third of the solvent was distilled off. The hot reaction mixture was filtered through a short layer of $NaHCO_3$, and after evaporation of the solvent, the crude product was purified by chromatography as above affording pure I (wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O) (1.200 g, 85%): mp 112 -114 °C;
$[\alpha]^{25}_D$ - 64.3 (*c* 0.8, $CDCl_3$);
^{1}H NMR (CDCl3) 7.62-7.59 (m, 2H), 7.41-7.24 (m, 8H), 5.16 (s, 1H), 4.92 (s, 1H), 4.61 (AB system, *J* = 11.0 Hz, 2H), 3.74 (s, 3 H), 3.46 (AB system, *J* = 25.2 Hz, 2H).
^{13}C NMR ($CDCl_3$); 169.0 (s), 165.4(s), 137.8 (s), 135.0 (s), 129.5 (d), 128.8 (d), 128.3 (d), 127.9, 127.8 (d), 125.4 (d), 107.7 (s), 79.1 (d), 78.3 (d), 55.5 (t), 52.6 (q), 48.6 (t)
IR($CDCl_3$): 1762, 1678 cm^{-1}
MS (m/z, %): 353 (M^+, 3), 147 (5), 120(36), 306 (13), 105 (80), 91 (100).

EXAMPLE 3

Preparation of *N*-(*p*-Methoxybenzyl)-*N*'-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-O-isopropylidenetartramic Acid Methyl Ester [compound IV, wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2]

[0033] A solution of II (wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$) (0.5 g, 2.09 mmol) in anhydrous CH_2Cl_2 (5 ml), III (wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (0.427 g, 2.09 mmol), PyBrOP (0.976 g, 2.09 mmol), and DIPEA (1.07 mL, 6.27 mmol) was treated as in the example 1. The crude product obtained was purified by chromatography (EtOAc-petroleum ether, 1:3, Rf 0.32), yielding IV (wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (0.370 g, 40%) as a colorless oil:
^{1}H NMR ($CDCl_3$): 7.90-7.85 (m, 2H), 7.61-7.43 (m, 3H), 7.21-7.15 (m, 2H), 6.90-6.82 (m, 2H), 5.39 (d, *J* = 5.1Hz, 1H), 5.13 (d, *J* = 5.1Hz, 1 H), 4.75 (m, 2H), 4.11 (m, 2H), 3.82 (s, 3 H), 3.79 (s, 3 H), 1.52 (s, 3 H), 1.36 (s, 3 H).

EXAMPLE 4

[0034] Preparation of Methyl (1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate [compound I wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O]

[0035] A solution of IV (wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (0.370 g, 0.84 mmol) in toluene (10 mL) was treated as reported in example 2. The crude product was purified by chromatography as above affording pure I (wherein R_1 = Ph, R_2 = H, R_3 = 4-MeO-$C_6H_4CH_2$, R_4 = H,

R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O) (0.177 g, 55 %): mp 134 - 136 °C;
$[\alpha]^{25}_D$ - 62.3 (c 0.6, $CDCl_3$);
^{1}H NMR (CDCl3) 7.62-7.59 (m, 2H), 7.41-7.24 (m, 5H), 7.11-6.91 (m, 2H), 5.14 (s, 1 H), 4.89 (s, 1 H), 4.24 (AB system, *J* = 11.0 Hz, 2H), 3.78 (s, 3 H), 3.74 (s, 3

[0036] H), 3.56 (AB system, *J* = 23.4 Hz, 2H).
^{13}C NMR ($CDCl_3$); 169.4 (s), 165.3(s), 159.8 (s), 137.8 (s), 135.0 (s), 129.5 (d), 128.1 (d), 127.1 (d), 126.4 (d), 119.2 (d), 107.1 (s), 79.8 (d), 78.0 (d), 58.5 (t), 55.1 (q), 52.6 (q), 48.1 (t).
IR ($CDCl_3$): 1768, 1682 cm^{-1}
MS (m/z, %): 383 (M^+, 5), 121 (100).

EXAMPLE 5

Preparation of (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-5-(4-hydroxyphenyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid [compound I wherein R_1 = 4-OH-C_6H_4, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = COOH, X = O, Z = O, Y = O]

[0037] Wang resin (1 g, 200-400 mesh, substitution 0.64 mmol/g) was suspended in CH_2Cl_2 (10 mL) and magnetically stirred for 15 min. After filtration, a solution of Ph_3P (1.024g, 3.904 mmol) and 4'-hydroxy-2-chloroacetophenone (compound V wherein Hal = Cl, R_1 = 4-OH-C_6H_4, R_2 = H), (0.568 g, 3.33 mmol) in a mixture of CH_2Cl_2 (10 mL) and Et_2O (4 mL) was added to the expanded resin. After 5 min, DEAD (607 mL, 3.904 mmol) was added drop-wise and the resulting suspension stirred at room temperature. After 24 h the suspension was filtered and the resin washed with DMF (3 x 10 mL), CH_2Cl_2 (3 x 10 mL), MeOH (3 x 10 mL) and again DMF (3 x 10 mL). Then, the resin (1.00 g), suspended in CH_2Cl_2 (1 mL), was treated with benzylamine (compound VI wherein R_3 = $PhCH_2$) (10 mL) and left under stirring at room temperature for 12 h. After filtration, the resin II (R_1 = Wang-4-OH-C_6H_4, R_2 = H, R_3 = $PhCH_2$) obtained was washed as above with DMF, CH_2Cl_2, MeOH and again DMF. Resin II (R_1 = Wang-4-OH-C_6H_4, R_2 = H, R_3 = $PhCH_2$) was then coupled with III [wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2] as follows: compound III (261 mg, 1.28 mmol) and PyBroP (597 mg, 1.28 mmol) were added to resin II (500 mg) suspended in DMF (10 mL), then DIPEA (438 µL, 1.28 mmol) was added slowly at room temperature and the resulting suspension stirred for 12 h. After the usual work-up, resin IV [R_1 = Wang-4-OH-C_6H_4, R_2 = H, R_3 = $PhCH_2$, R_4=R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2] was obtained. The cyclization step was performed on 250 mg of resin IV as follows: resin IV (250 mg) and *p*-TsOH (6 mg) were suspended in toluene and the mixture refluxed for 15 min. Then part of the solvent (25 mL) was distilled off and the residual suspension filtered. The solution was concentrated obtaining, as a yellow oil, compound I [wherein R_1 = 4-OH-C_6H_4, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = COOH, X = O, Z = O, Y = O] (33 mg). with complete cleavage from the resin.
^{1}H NMR ($CDCl_3$) δ: 7.78 (d, *J* = 8.8 Hz, 2 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.40-7.00 (m, 3 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.13 (s, 1 H), 4.86 (s, 1H), 4.58 (AB system, *J* = 15.0 Hz, 2 H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.38 (d, *J* = 11.8 Hz, 1H).

EXAMPLE 6

Preparation of *N*-(4-methylphenyl)-*N*-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-O-isopropylidenetartramic Acid Methyl Ester [compound IV wherein R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4, R_4=H, R_5= H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2]

[0038] To a solution of III (wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (366 mg, 1.8 mmol) in methylene chloride (1.8 ml) and PyBrop (839 mg, 1.8 mmol) was added II (wherein R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4) (406mg, 1.8 mmol) and DIPEA (0.765 mL, 3.6 mmol). The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (AcOEt- Petroleum Ether. 1:2, R_f = 0.37) to give IV (R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4, R_4=R_5= H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) as yellow oil (440 mg, 62%).
^{1}H NMR δ 8.00-7.90 (m, 2H), 7.62-7.39 (m, 4H), 7.36-7.12 (m, 3H), 5.26 (*J*=17.2 Hz part A of AB system, 1H) 4.96 (*J*=17.2 Hz part B of AB system, 1H), 5.07 (*J*=6.6 Hz part A of AB system, 1 H) 4.66 (*J*=6.6 Hz part B of AB system, 1 H),3.74 (s, 3H), 2.36 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H). MS (m/z, %): 411 (M^+, 4), 352 (6), 306 (13), 120(100).

EXAMPLE 7

Preparation of Methyl (1*R*,5*S*,7*R*)-3-(4'-methylphenyl)-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate [compound I wherein R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O]

[0039] A solution of IV (prepared in the example 6, wherein R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4, R_4=H, R_5= H, R_6 =

COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (310 mg, 0.75 mmol) in toluene (32 ml) was quickly added to a refluxing solution of H_2SO_4/SiO_2 (175 mg) in toluen (16 ml). The mixture was treated as reported in Example 2. The product I [wher In R_1 = Ph, R_2 = H, R_3 = 4-Me-C_6H_4, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O] was obtained in pure form (260 mg, 97%).

^{1}H NMR δ: 7.78-7.66 (m, 2H), 7.48-7.36 (m, 4H), 7.30-7.10 (m, 3H), 5.23 (s, 1 H), 5.02 (s, 1H), 4.02 (J=12 Hz part A of AB system, 1H) 3.90 (J=12 Hz part B of AB system, 1H), 3.73 (s, 3H), 2.35 (s, 3H).^{13}C NMR δ: 168.9(s), 165.1(s), 137.4 (s), 136.8 (s), 135.1(s), 129.9 (d), 129.6 (d), 128.4 (d), 125.4 (d), 125.3(d), 107.6 (s),79.4 (d), 78.4 (d), 59.2 (t), 52.7 (q), 20.9 (q). MS (m/z, %): 353 (M^+,4), 294 (2), 119 (100).

EXAMPLE 8

Preparation of *N*-[(1 S)-(1-carbomethoxy-2-phenylethyl)]-*N*'-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4=H, R_5= H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2].

[0040] To a solution of III (wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (118 mg, 0.58 mmol) in CH_2Cl_2 (0.5 mL), and PyBrOP (270 mg, 0.58 mmol) was added II (wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe) CH_2Ph) (120 mg, 0.4 mmol) and DIPEA (0.255 mL, 1.2 mmol). The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (CH_2Cl_2- MeOH (40:1) to afford IV (wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4=H, R_5 = H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (160mg, 82%).

[0041] The ^{1}H and ^{13}C NMR spectrums show two set of signals in 2:1 ratio.^{1}H NMR ($CDCl_3$) δ: 8.04-7.90 (m, 2H), 7.70-7.42 (m,.4H), 7.38-7.20 (m, 4H), 5.48-4.74 (m, 5H), 3.76 and 3.75 (s,3H), 3.59 (s,3H), 3.38-3.30 (m, 2H), 1.56 and 1.46, 1.33, 1.28 (s, 6H). ^{13}C NMR ($CDCl_3$) δ:193.6, 192.3, 170.7, 170.6, 169.9, 169.4, 168.5, 136.6, 135.9, 135.0, 134.5, 133.7, 129.1, 129.0, 128.7, 128.5, 128.4, 128.3, 127.8, 127.6, 126.8, 126.6, 113.2, 77.2, 76.9, 75.4, 60.3, 59.3, 52.5, 52.3, 51.7, 49.2, 36.4, 35.6, 26.5, 26.3, 26.2, 25.9. MS m/z (%): 483 (M+, 2), 424 (4), 378 (7), 320 (16), 206 (34), 192 (50), 162 (63), 105 (100)

EXAMPLE 9

Preparation of Methyl (1*R*,5*S*,7*R*)-3-[(1S)-1-carbomethoxy-2-phenylethyl]-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo [3.2.1]octane-7-exo-carboxylate [compound I wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O]

[0042] A solution of IV (prepared according the example 8, wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4=H, R_5= H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2) (150 mg, 0.30 mmol) in toluene (5 ml) was quickly added to a refluxing solution of H_2SO_4/SiO_2 (60 mg) in toluene (33 ml) The mixture was treated as reported in Example 2. The crude product was purified by flash chromatography (AcOEt-Petroleum Ether 1:1, R_f = 0.41) to afford I (wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O) as 2:1 mixture of pimers (82 mg, 65%).

^{1}H NMR ($CDCl_3$) major epimer: δ 7.60 (m, 2 H), 7.90-7.30 (m, 8 H), 5.11 (dd, *J*= 5.6, 10.8 Hz, 1 H), 4.99 (s, 1 H), 4.84 (s 1 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.75-3.34 (m, 3 H), 3.08 (m, 1 H).
MS m/z (%):425 (M^+, 2), 366 (19), 306 (7), 192 (32), 105 (100), 91 (88), 77 (62).

EXAMPLE 10

Preparation of N-Boc *N*-(4-methyoxybenzyl)-*N*'-[2-oxo-2-phenylethyl]threoninamide IV (wherein R_1 = Ph, R_2 = H, R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6=Me, R_7 = Boc, R_8 = H, Z = N, Y = O).

[0043] To a solution of III (R_4 = H, R_5 = H, R_6 = Me, R_7 = Boc, R_8 = H, Z = N, Y = O) in CH_2Cl_2 (5 mL) and PyBrOP (531 mg, 1.14 mmol) was added II (wherein R_1 = Ph, R_2 = H, R_3 = *p*-CH_3O-$C_6H_4CH_2$) (333 mg, 1.14 mmol) and DIPEA (0.585 mL, 3.42 mmol). The mixture The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (EtOAc-petrolrum ether, 1:1.5, R_f = 0.23) to afford IV (wherein R_1 = Ph, R_2 = H, R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = Me, R_7 = Boc, R_8 = H, Z = N, Y = O) (232 mg, 44%) as an oil.

^{1}H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 7.85 (d, *J* = 7.3 Hz, 2 H), 7.55 (m, 1 H), 7.42 (m, 2 H), 7.11(m, 2 H), 6.82 (m, 2 H), 5.50 (m, 1 H), 5.29 (d, *J* = 14.3 Hz, 1 H), 5.00-4.20 (m, 5 H), 4.00 (m, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 1.38 (s, 9 H), 1.31 (s, 9 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 1.07 (d, *J* = 6.2 Hz, 3 H).

EXAMPLE 11

Preparation of (1*R*,5*S*,7*R*)-3-(4-methoxybenzyl)-2-oxo-5-phenyl-7-exo-methyl-6 oxa-3,8-diazabicyclo[3.2.1]octane [compound I wherein R_1 = Ph, R_2 = H R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = Me, X = O, Z = N, Y = O]

[0044] A solution of IV (wh rein R_1 = Ph, R_2 = H, R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = Me, R_7 = Boc, R_8 = H, Z = N, Y = O) (78.3 mg, 0.172 mmol) and *p*-TsOH (36 mg, 0.189 mmol) in benzene (10 ml) is refluxed for 30 min, then 8 ml of solvent were distilled off. The resulting solution was concentrated obtaining compound I (I wherein R_1 = Ph, R_2 = H R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = Me, X = O, Z = N, Y = O) as p-TsOH salt (60 mg, 76%). This was treated with 0.1 M aqueous solution of KOH end the free amine extracted with $CHCl_3$ to give, after concentration, compound I (I wherein R_1 = Ph, R_2 = H R_3 = *p*-CH_3O-$C_6H_4CH_2$, R_4 = H, R_5 = H, R_6 = Me, X = O, Z = N, Y = O) as a colorless oil (41 mg, 70%).
^{1}H NMR ($CDCl_3$) δ 7.70 (m, 2 H), 7.52-7.20 (m, 5 H), 6.83 (m, 2 H), 5.07 (s, 1 H), 4.79 (d, *J* = 14.1 Hz, 1 H), 4.55 (d, *J* = 14.1 Hz, 1 H), 3.78 (s, 3 H), 3.78 (m, 2 H), 2.84 (q, *J* = 7.4 Hz, 1 H), 1.60 (d, *J* = 7.4 Hz, 3 H).

EXAMPLE 12

Preparation of (1*S*,5*S*,7*S*)-3-benzyl-5-phenyl-7-exo-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane [compound I wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = CH_2OH, X = H , Z = O, Y = O]

[0045] To a suspension of $LiAlH_4$ (50 mg, mmol) in anhydrous THF (10 mL) was added dropwise at 0 °C and under nitrogen atmosphere a solution of compound I, [prepared according the example 2, wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O] (22 mg, 0.568 mmol) in dry THF (12 ml). The mixture was r fluxed for 2h, and then, after cooling to 0 °C, diethyl ether (2 mL) were added. The mixture was filtered through a short layer of anhydrous Na_2SO_4, and the residue was suspended in 1 M KOH solution (30 mL), saturated with NaCl, and extracted with Et_2O and EtOAc. The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated to give compound I (wherein R_1 = Ph, R_2 = H, R_3 = $PhCH_2$, R_4 = H, R_5 = H, R_6 = CH_2OH, X = H , Z = O, Y = O) as a colorless oil (35 mg, 0.112 mmol, 79 %).
^{1}H NMR ($CDCl_3$) δ 7.53-7.30 (m, 2 H), 7.29-7.23 (m, 8 H), 4.66-4.34 (m, 2 H), 3.34-3.46 (m, 4 H), 3.06-2.43 (m. 4 H), 1.82 (br s, 1 H).

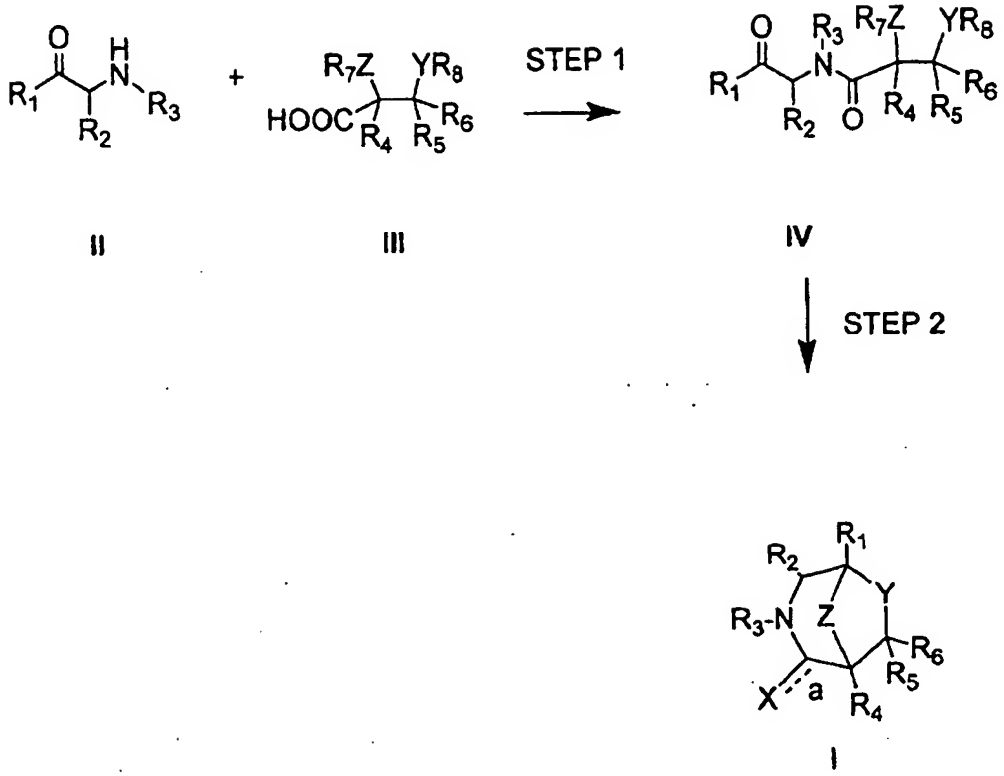
EXAMPLE 13

Preparation of Methyl (1*R*,5*S*,7*R*)-3-[(1*S*)-1-carbomethoxy-2-phenylethyl]-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo [3.2.1]octane-7-*exo*-carboxylate [compound I wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O]

[0046] Fmoc-(S)-phenylalanine-O-Wang resin (2 g, 200-400 mesh, substitution 1 mmol/g) was treated with piperidine (30%) in DMF (10 mL) under stirring, for 15 min, to obtain compound VI [wherein R_3 =CH(COO-Wang resin)CH_2Ph]. After filtration, the resin suspended in DMF (10 mL), was treated with 2-bromo-acetophenone (compound V wherein Hal = Br, R_1 = Ph, R_2 = H), (1.09 g, 6.0 mmol) and DIPEA (340 µL, 2 mmol) and left under stirring at room temperature for 48 h. The resin II [R_1 =Ph, R_2 = H R_3 =CH(COO-Wang resin)CH_2Ph] obtained was washed as reported in example 5 with DMF, CH_2Cl_2, MeOH and again DMF. Resin II [R_1 = Ph, R_2 = H R_3 =CH(COO-Wang resin)CH_2Ph] was then coupled with III [wherein R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2] as follows: compound III (816 mg, 4 mmol) and PyBroP (1.86 g, 4 mmol) were added to resin II (1.00 g) suspended in DMF (10 mL), then DIPEA (680 µL, 4 mmol) was added slowly at room temperature and the resulting suspension stirred for 12 h. After the usual work-up, resin IV [R_1 = Ph, R_2 = H, R_3 =CH(COO-Wang resin)CH_2Ph, R_4=H, R_5=H, R_6 = COOMe, Z = O, Y = O, R_7—R_8 = CH_2-CH_2] was obtained. The cyclization step was performed on 1 g of resin IV as follows: resin IV (1 g) and *p*-TsOH (95 mg) were suspended in toluene and the mixture refluxed for 15 min. Then part of the solvent (50 mL) was distilled off and the residual suspension filtered. The solution was concentrated obtaining, a solid residue (170 mg) contaning compound I [wherein R_1 = Ph, R_2 = H, R_3 = CH(COOH)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOH, X = O, Z = O, Y = O].

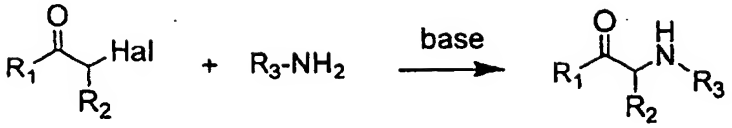
[0047] Crude compound I [wherein R_1 = Ph, R_2 = H, R_3 = CH(COOH)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOH, X = O, Z = O, Y = O] treated with solution of diazomethane in ether gave compound I [wherein R_1 = Ph, R_2 = H, R_3 = CH(COOMe)CH_2Ph, R_4 = H, R_5 = H, R_6 = COOMe, X = O, Z = O, Y = O] identical with the product (major epimer) as described in example 8.

Scheme 1



II III IV I

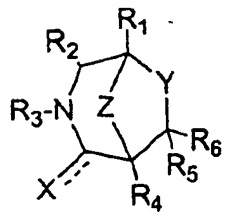
Scheme 2



V VI II

Claims

1. Heterobicycle derivatives of general formula (I)



I

wherein:

R_1, is chosen in the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; RR'N-C_{1-8}alkyl, RR'N-aryl, RO-aryl, R(O)C-aryl, RO(O)C-aryl, RR'N(O)C-aryl, (P)-W-NR-aryl, (P)-W-O-aryl, (P)-W-C(O)O-aryl, (P)-W-O(O)C-aryl, (P)-W-C(O)RN-aryl, (P)-W-NR(O)C-aryl;
R_2, is chosen in the group consisting of H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; aminoC_{1-8}alkyl, aminoaryl, C_{1-8}alkyloxyaryl, hydroxyaryl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl,-(side chain), -(side chain)-W-(P) or
R_1 and R_2 taken together are a C_{1-4}alkyl, C_{2-4}alkenyl, cycloalkyl, benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms;
R_3, is chosen in the group consisting H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; RR'NC_{1-8}alkyl, RR'Naryl, RO-C_{1-8}alkyl,
RO(O)C-C_{1-8}alkyl, R(O)C-C_{1-8}alkyl, RC(O)O-C_{1-8}alkyl, RC(O)N(R)C_{1-8}alkyl RO-aryl, RO(O)C-aryl, R(O)C-aryl RC(O)O-aryl, RC(O)N(R)aryl, -CH(amino acid side-chain)CO_2R, -CH(amino acid side-chain)C(O)NR, -CH(amino acid side-chain)-C(O)O-W-(P), -CH(amino acid side-chain)-C(O)N(R)-W-(P), CH(CO_2R)-amino acid side-chain-W-(P), CH(CONRR')-amino acid side-chain-W-(P), protecting group;
R_4 and R_5, same or different, are chosen in the group consisting H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl;
R_6 is chosen in the group consisting, H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, arylC_{1-8}alkyl, heterocycle, heterocycleC_{1-8}alkyl; -C(O)R, -C(O)OR, -C(O)NRR', CH_2OR, CH_2NRR', -C(O)NH-CH(amino acid side-chain)C(O)OR, -C(O)O-W-(P), -C(O)N(R)-W-(P), -CH_2O-W-(P), -CH_2N(R)-W-(P);
R and R', same or different, are chosen in the group consisting of: H, C_{1-8}alkyl,
C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl; heterocycleC_{1-8}alkyl; a protecting group, -C(O)CH-(amino acid side-chain)-NHR, -NH-CH(amino acid side-chain)COOR, -CH(amino acid side-chain)COOR;
P is resin, both soluble or bound to a solid support;
W is as linker;
X is O, S, when a is a double bond, or X is H and a is single bond,
Y and Z, same or different, are O, S, SO, SO_2, N-R, wherein R is as above defined;

the above said alkyl-, alkenyl-, alkinyl-, cycloalkyl-, aryl- and heterocycle-groups, being possibly substituted.

2. Heterobicycle derivatives according to Claim 1 wherein:

the resin P is a polymeric material soluble in the solvents commonly used in organic synthesis or bound to a solid support;
the solid support is a solid material (at room temperature) to which starting resin materials (reactive groups) may be bound;
W is a molecule capable of binding the resin P to the reagents and the products of formula (I);
Protecting group means any group capable of preventing the atom to which it is attached from participating in an undesired reaction or bonding, as commonly used in synthesis reactions.
Amino acid side-chain means the side chain moieties of the natural occurring L or D amino acids or the non naturally occurring amino acids; and the other substituents are as definied in Claim 1.

3. Heterobicycle derivatives according to Claim 2 wherein:

the resin is a polymeric material derivatised with a -NH_2 group or an hydroxyl group possibly bound to a solid support materials chosen among polyethylene and polystyrene compounds and relat d inert polymeric compounds;
prot cting groups ar those which prevent reaction or bonding of oxygen, nitrogen, carboxylic acids, thiols, alcohols, amin s and th like;

the amino acid side-chain is the side chain of a naturally or non naturally occurring amino acid and the other substituents are as defined in Claim 1.

4. Heterobicycle derivatives according to Claim 3 wherein the non naturally occurring amino acids are chosen among. norleucine (Nle), norvaline (NVa), β-alanine, L or D α-phenyl glycine and the like and the other substituents are as described in Claim 1.

5. Heterobicycle derivatives according to Claim 4 represented by the following formulae:

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
1.	O	O	O	Ph	H	$PhCH_2$	H	H	COOH
2.	O	O	O	4-HO-Ph	H	$PhCH_2$	H	H	COOH
3.	O	O	O	4-O_2N-Ph	H	$PhCH_2$	H	H	COOH
4.	O	O	O	4-H_2N-Ph	H	$PhCH_2$	H	H	COOH
5.	O	O	O	4-MeO(O)C-Ph	H	$PhCH_2$	H	H	COOH
6.	O	O	O	4-Me-Ph	H	$PhCH_2$	H	H	COOH
7.	O	O	O	4-MeO-Ph	H	$PhCH_2$	H	H	COOH
8.	O	O	O	4-Cl-Ph	H	$PhCH_2$	H	H	COOH
9.	O	O	O	4-Br-Ph	H	$PhCH_2$	H	H	COOH
10.	O	O	O	2-HO-Ph	H	$PhCH_2$	H	H	COOH
11.	O	O	O	2-O_2N-Ph	H	$PhCH_2$	H	H	COOH
12.	O	O	O	2-H_2N-Ph	H	$PhCH_2$	H	H	COOH
13.	O	O	O	2-MeO(O)C-Ph	H	$PhCH_2$	H	H	COOH
14.	O	O	O	2-Me-Ph	H	$PhCH_2$	H	H	COOH
15.	O	O	O	2-MeO-Ph	H	$PhCH_2$	H	H	COOH
16.	O	O	O	2-Cl-Ph	H	$PhCH_2$	H	H	COOH
17.	O	O	O	2-Br-Ph	H	$PhCH_2$	H	H	COOH
18.	O	O	O	2-Nafthyl	H	$PhCH_2$	H	H	COOH
19.	O	O	O	2-thienyl	H	$PhCH_2$	H	H	COOH
20.	O	O	O	4-biphenyl	H	$PhCH_2$	H	H	COOH
21.	O	O	O	Ph	H	Me	H	H	COOH
22.	O	O	O	Ph	H	$CH_3(CH_2)_2$	H	H	COOH
23.	O	O	O	Ph	H	cyclohexyl	H	H	COOH
24.	O	O	O	Ph	H	allyl	H	H	COOH
25.	O	O	O	Ph	H	Ph	H	H	COOH
26.	O	O	O	Ph	H	4-HO-Ph	H	H	COOH
27.	O	O	O	Ph	H	4-O_2N-Ph	H	H	COOH
28.	O	O	O	Ph	H	4-MeO_2C-Ph	H	H	COOH
29.	O	O	O	Ph	H	4-Me-Ph	H	H	COOH
30.	O	O	O	Ph	H	4-MeO-Ph	H	H	COOH
31.	O	O	O	Ph	H	4-Cl-Ph	H	H	COOH
32.	O	O	O	Ph	H	4-Br-Ph	H	H	COOH
33.	O	O	O	Ph	H	2-HO-Ph	H	H	COOH
34.	O	O	O	Ph	H	2-O_2N-Ph	H	H	COOH
35.	O	O	O	Ph	H	2-MeO_2C-Ph	H	H	COOH
36.	O	O	O	Ph	H	2-Me-Ph	H	H	COOH
37.	O	O	O	Ph	H	2-MeO-Ph	H	H	COOH

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
38.	O	O	O	Ph	H	2-Cl-Ph	H	H	COOH
39.	O	O	O	Ph	H	2-Br-Ph	H	H	COOH
40.	O	O	O	Ph	H	2-Nafthyl	H	H	COOH
41.	O	O	O	Ph	H	2-thienyl	H	H	COOH
42.	O	O	O	Ph	H	4-biphenyl	H	H	COOH
43.	O	O	O	Ph	H	4-MeO_2C-$PhCH_2$	H	H	COOH
44.	O	O	O	Ph	H	4-Me-$PhCH_2$	H	H	COOH
45.	O	O	O	Ph	H	4-MeO$PhCH_2$	H	H	COOH
46.	O	O	O	Ph	H	4-Cl-$PhCH_2$	H	H	COOH
47.	O	O	O	Ph	H	4-Br-$PhCH_2$	H	H	COOH
48.	O	O	O	Ph	H	2-HO-$PhCH_2$	H	H	COOH
49.	O	O	O	Ph	H	2-O_2N-$PhCH_2$	H	H	COOH
50.	O	O	O	Ph	H	2-MeO_2C-$PhCH_2$	H	H	COOH
51.	O	O	O	Ph	H	2-Me-$PhCH_2$	H	H	COOH
52.	O	O	O	Ph	H	2-MeO-$PhCH_2$	H	H	COOH
53.	O	O	O	Ph	H	2-Cl-$PhCH_2$	H	H	COOH
54.	O	O	O	Ph	H	2-Br-$PhCH_2$	H	H	COOH
55.	O	O	O	4-HO-Ph	H	4-HO-Ph CH_2	H	H	COOH
56.	O	O	O	4-HO-Ph	H	4-O_2N-$PhCH_2$	H	H	COOH
57.	O	O	O	4-HO-Ph	H	4-MeO_2C-$PhCH_2$	H	H	COOH
58.	O	O	O	4-HO-Ph	H	4-Me-$PhCH_2$	H	H	COOH
59.	O	O	O	4-HO-Ph	H	4-MeO$PhCH_2$	H	H	COOH
60.	O	O	O	4-HO-Ph	H	4-Cl-$PhCH_2$	H	H	COOH
61.	O	O	O	4-HO-Ph	H	4-Br-$PhCH_2$	H	H	COOH
62.	O	O	O	4-HO-Ph	H	2-HO-$PhCH_2$	H	H	COOH
63.	O	O	O	4-HO-Ph	H	2-O_2N-$PhCH_2$	H	H	COOH
64.	O	O	O	4-HO-Ph	H	2-MeO_2C-$PhCH_2$	H	H	COOH
65.	O	O	O	4-HO-Ph	H	2-Me-$PhCH_2$	H	H	COOH
66.	O	O	O	4-HO-Ph	H	2-MeO-$PhCH_2$	H	H	COOH
67.	O	O	O	4-HO-Ph	H	2-Cl-$PhCH_2$	H	H	COOH
68.	O	O	O	4-HO-Ph	H	2-Br-$PhCH_2$	H	H	COOH
69.	O	O	O	4-HO-Ph	H	Me	H	H	COOH
70.	O	O	O	4-HO-Ph	H	$CH_3(CH_2)_2$	H	H	COOH
71.	O	O	O	4-HO-Ph	H	cyclohexyl	H	H	COOH
72.	O	O	O	4-HO-Ph	H	allyl	H	H	COOH
73.	O	O	O	Ph	H	HO_2C-CH_2	H	H	COOH
74.	O	O	O	Ph	H	Bn(HO_2C)CH	H	H	COOH
75.	O	O	O	Ph	H	$HOCH_2$(HO_2C)CH	H	H	COOH
76.	O	O	O	Ph	H	CH_3(HO)CH(HO_2C)CH	H	H	COOH
77.	O	O	O	Ph	H	MeS$(CH_2)_2$(HO_2C)CH	H	H	COOH
78.	O	O	O	Ph	H	$H_2N(CH_2)_3$(HO_2C)CH	H	H	COOH
79.	O	O	O	Ph	H	HO_2CCH_2(HO_2C)CH	H	H	COOH
80.	O	O	O	Ph	H	imidazole-CH_2(HO_2C)CH	H	H	COOH
81.	O	O	O	Ph	H	indole-CH_2(HO_2C)CH	H	H	COOH
82.	O	O	O	4-HO-Ph	H	HO_2C-CH_2	H	H	COOH
83.	O	O	O	4-HO-Ph	H	Me(HO_2C)CH	H	H	COOH
84.	O	O	O	4-HO-Ph	H	$(CH_3)_2$CH(HO_2C)CH	H	H	COOH
85.	O	O	O	4-HO-Ph	H	Bn(HO_2C)CH	H	H	COOH
86.	O	O	O	4-HO-Ph	H	$HOCH_2$(HO_2C)CH	H	H	COOH

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
87.	O	O	O	4-HO-Ph	H	$CH_3(HO)CH(HO_2C)CH$	H	H	COOH
88.	O	O	O	4-HO-Ph	H	$MeS(CH_2)_2(HO_2C)CH$	H	H	COOH
89.	O	O	O	4-HO-Ph	H	$H_2N(CH_2)_3(HO_2C)CH$	H	H	COOH
90.	O	O	O	4-HO-Ph	H	$HO_2CCH_2(HO_2C)CH$	H	H	COOH
91.	O	O	O	4-HO-Ph	H	imidazole-$CH_2(HO_2C)CH$	H	H	COOH
92.	O	O	O	4-HO-Ph	H	indole-$CH_2(HO_2C)CH$	H	H	COOH
93.	O	O	O	Ph	Me	$PhCH_2$	H	H	COOH
94.	O	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	COOH
95.	O	O	O	Ph	Bn	$PhCH_2$	H	H	COOH
96.	O	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	COOH
97.	O	O	O	Ph	Me	$HO_2C\text{-}CH_2$	H	H	COOH
98.	O	O	O	4-HO-Ph	Me	$HO_2C\text{-}CH_2$	H	H	COOH
99.	O	O	O	Ph	Bn	$HO_2C\text{-}CH_2$	H	H	COOH
100.	O	O	O	4-HO-Ph	Bn	$HO_2C\text{-}CH_2$	H	H	COOH
101.	O	O	O	Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
102.	O	O	O	4-HO-Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
103.	O	HN	O	Ph	H	$PhCH_2$	H	H	CH_3
104.	O	HN	O	Ph	Me	$PhCH_2$	H	H	CH_3
105.	O	HN	O	Ph	Bn	$PhCH_2$	H	H	CH_3
106.	O	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	CH_3
107.	O	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	CH_3
108.	O	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	CH_3
109.	O	HN	O	Ph	H	Ph	H	H	CH_3
110.	O	HN	O	Ph	Me	Ph	H	H	CH_3
111.	O	HN	O	Ph	Bn	Ph	H	H	CH_3
112.	O	HN	O	4-OH-Ph	H	Ph	H	H	CH_3
113.	O	HN	O	4-OH-Ph	Me	Ph	H	H	CH_3
114.	O	HN	O	4-OH-Ph	Bn	Ph	H	H	CH_3
115.	O	HN	O	Ph	H	CH_3-Ph	H	H	CH_3
116.	O	HN	O	Ph	Me	CH_3-Ph	H	H	CH_3
117.	O	HN	O	Ph	Bn	CH_3-Ph	H	H	CH_3
118.	O	HN	O	4-OH-Ph	H	CH_3-Ph	H	H	CH_3
119.	O	HN	O	4-OH-Ph	Me	CH_3-Ph	H	H	CH_3
120.	O	HN	O	4-OH-Ph	Bn	CH_3-Ph	H	H	CH_3
121.	O	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
122.	O	HN	O	Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
123.	O	HN	O	Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
124.	O	HN	O	4-OH-Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
125.	O	HN	O	4-OH-Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
126.	O	HN	O	4-OH-Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
127.	O	HN	O	Ph	H	CH_3-$PhCH_2$	H	H	CH_3
128.	O	HN	O	Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
129.	O	HN	O	Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
130.	O	HN	O	4-OH-Ph	H	CH_3-$PhCH_2$	H	H	CH_3
131.	O	HN	O	4-OH-Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
132.	O	HN	O	4-OH-Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
133.	O	HN	O	Ph	H	Me	H	H	CH_3
134.	O	HN	O	Ph	H	$CH_3(CH_2)_2$	H	H	CH_3
135.	O	HN	O	Ph	H	cyclohexyl	H	H	CH_3

(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
136.	O	HN	O	Ph	H	allyl	H	H	CH_3
137.	O	HN	O	4-OH-Ph	H	Me	H	H	CH_3
138.	O	HN	O	4-OH-Ph	H	$CH_3(CH_2)_2$	H	H	CH_3
139.	O	HN	O	4-OH-Ph	H	cyclohexyl	H	H	CH_3
140.	O	HN	O	4-OH-Ph	H	allyl	H	H	CH_3
141.	O	HN	O	Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
142.	O	HN	O	Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
143.	O	HN	O	Ph	Bn	$HO_2C\text{-}CH_2$	H	H	CH_3
144.	O	HN	O	4-OH-Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
145.	O	HN	O	4-OH-Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
146.	O	HN	O	4-OH-Ph	Bn	$HO_2C\text{-}CH_2$	H	H	CH_3
147.	O	HN	O	Ph	H	$Bn(HO_2C)CH$	H	H	CH_3
148.	O	HN	O	Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
149.	O	HN	O	Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
150.	O	HN	O	4-OH-Ph	H	$Bn(HO_2C)CH$	H	H	CH_3
151.	O	HN	O	4-OH-Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
152.	O	HN	O	4-OH-Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
153.	H	O	O	Ph	H	$PhCH_2$	H	H	COOH
154.	H	O	O	Ph	Me	$PhCH_2$	H	H	COOH
155.	H	O	O	Ph	Bn	$PhCH_2$	H	H	COOH
156.	H	O	O	4-HO-Ph	H	$PhCH_2$	H	H	COOH
157.	H	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	COOH
158.	H	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	COOH
159.	H	O	O	Ph	H	$HO_2C\text{-}CH_2$	H	H	COOH
160.	H	O	O	Ph	Me	$HO_2C\text{-}CH_2$	H	H	COOH
161.	H	O	O	Ph	Bn	$HO_2C\text{-}CH_2$	H	H	COOH
162.	H	O	O	4-HO-Ph	H	$HO_2C\text{-}CH_2$	H	H	COOH
163.	H	O	O	4-HO-Ph	Me	$HO_2C\text{-}CH_2$	H	H	COOH
164.	H	O	O	4-HO-Ph	Bn	$HO_2C\text{-}CH_2$	H	H	COOH
165.	H	O	O	Ph	H	$Bn(HO_2C)CH$	H	H	COOH
166.	H	O	O	Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
167.	H	O	O	Ph	Bn	$Bn(HO_2C)CH$	H	H	COOH
168.	H	O	O	4-HO-Ph	H	$Bn(HO_2C)CH$	H	H	COOH
169.	H	O	O	4-HO-Ph	Me	$Bn(HO_2C)CH$	H	H	COOH
170.	H	O	O	4-HO-Ph	Bn	$Bn(HO_2C)CH$	H	H	COOH
171.	H	HN	O	Ph	H	$PhCH_2$	H	H	CH_3
172.	H	HN	O	Ph	H	$4\text{-MeO-}PhCH_2$	H	H	CH_3
173.	H	HN	O	Ph	Me	$PhCH_2$	H	H	CH_3
174.	H	HN	O	Ph	Bn	$PhCH_2$	H	H	CH_3
175.	H	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	CH_3
176.	H	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	CH_3
177.	H	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	CH_3
178.	H	HN	O	Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
179.	H	HN	O	Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
180.	H	HN	O	Ph	Bn	$HO_2C\text{-}CH2$	H	H	CH_3
181.	H	HN	O	4-OH-Ph	H	$HO_2C\text{-}CH_2$	H	H	CH_3
182.	H	HN	O	4-OH-Ph	Me	$HO_2C\text{-}CH_2$	H	H	CH_3
183.	H	HN	O	4-OH-Ph	Bn	$HO_2C\text{-}CH_2$	H	H	CH_3
184.	H	HN	O	Ph	H	$Bn(HO_2C)CH$	H	H	CH_3

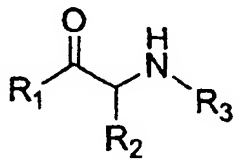
(continued)

Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
185.	H	HN	O	Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
186.	H	HN	O	Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
187.	H	HN	O	4-OH-Ph	H	$Bn(HO_2C)CH$	H	H	CH_3
188.	H	HN	O	4-OH-Ph	Me	$Bn(HO_2C)CH$	H	H	CH_3
189.	H	HN	O	4-OH-Ph	Bn	$Bn(HO_2C)CH$	H	H	CH_3
190.	H	HN	O	Ph	H	Ph	H	H	CH_3
191.	H	HN	O	Ph	Me	Ph	H	H	CH_3
192.	H	HN	O	Ph	Bn	Ph	H	H	CH_3
193.	H	HN	O	4-OH-Ph	H	Ph	H	H	CH_3
194.	H	HN	O	4-OH-Ph	Me	Ph	H	H	CH_3
195.	H	HN	O	4-OH-Ph	Bn	Ph	H	H	CH_3
196.	H	HN	O	Ph	H	CH_3-Ph	H	H	CH_3
197.	H	HN	O	Ph	Me	CH_3-Ph	H	H	CH_3
198.	H	HN	O	Ph	Bn	CH_3-Ph	H	H	CH_3
199.	H	HN	O	4-OH-Ph	H	CH_3-Ph	H	H	CH_3
200.	H	HN	O	4-OH-Ph	Me	CH_3-Ph	H	H	CH_3
201.	H	HN	O	4-OH-Ph	Bn	CH_3-Ph	H	H	CH_3
202.	H	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
203.	H	HN	O	Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
204.	H	HN	O	Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
205.	H	HN	O	4-OH-Ph	H	4-MeO-$PhCH_2$	H	H	CH_3
206.	H	HN	O	4-OH-Ph	Me	4-MeO-$PhCH_2$	H	H	CH_3
207.	H	HN	O	4-OH-Ph	Bn	4-MeO-$PhCH_2$	H	H	CH_3
208.	H	HN	O	Ph	H	CH_3-$PhCH_2$	H	H	CH_3
209.	H	HN	O	Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
210.	H	HN	O	Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
211.	H	HN	O	4-OH-Ph	H	CH_3-$PhCH_2$	H	H	CH_3
212.	H	HN	O	4-OH-Ph	Me	CH_3-$PhCH_2$	H	H	CH_3
213.	H	HN	O	4-OH-Ph	Bn	CH_3-$PhCH_2$	H	H	CH_3
214.	H	O	O	Ph	H	$PhCH_2$	H	H	CH_2OH
215.	H	O	O	Ph	H	4-MeO$PhCH_2$	H	H	CH_2OH
216.	H	O	O	Ph	Me	$PhCH_2$	H	H	CH_2OH
217.	H	O	O	Ph	Bn	$PhCH_2$	H	H	CH_2OH
218.	H	O	O	4-HO-Ph	H	$PhCH_2$	H	H	CH_2OH
219.	H	O	O	4-HO-Ph	Me	$PhCH_2$	H	H	CH_2OH
220.	H	O	O	4-HO-Ph	Bn	$PhCH_2$	H	H	CH_2OH
221.	H	O	O	Ph	H	$HOCH_2$	H	H	CH_2OH
222.	H	O	O	Ph	Me	$HOCH_2$	H	H	CH_2OH
223.	H	O	O	Ph	Bn	$HOCH_2$	H	H	CH_2OH
224.	H	O	O	4-HO-Ph	H	$HOCH_2$	H	H	CH_2OH
225.	H	O	O	4-HO-Ph	Me	$HOCH_2$	H	H	CH_2OH
226.	H	O	O	4-HO-Ph	Bn	$HOCH_2$	H	H	CH_2OH
227.	H	O	O	Ph	H	$Bn(HOH_2C)CH$	H	H	CH_2OH
228.	H	O	O	Ph	Me	$Bn(HOH_2C)CH$	H	H	CH_2OH
229.	H	O	O	Ph	Bn	$Bn(HOH_2C)CH$	H	H	CH_2OH
230.	H	O	O	4-HO-Ph	H	$Bn(HOH_2C)CH$	H	H	CH_2OH
231.	H	O	O	4-HO-Ph	Me	$Bn(HOH_2C)CH$	H	H	CH_2OH
232.	H	O	O	4-HO-Ph	Bn	$Bn(HOH_2C)CH$	H	H	CH_2OH
233.	H	HN	O	Ph	H	$PhCH_2$	H	H	H

(continued)

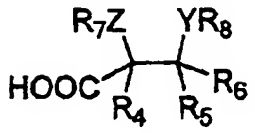
Comp.	X	Z	Y	R_1	R_2	R_3	R_4	R_5	R_6
234.	H	HN	O	Ph	H	4-MeO-$PhCH_2$	H	H	H
235.	H	HN	O	Ph	M	$PhCH_2$	H	H	H
236.	H	HN	O	Ph	Bn	$PhCH_2$	H	H	H
237.	H	HN	O	4-OH-Ph	H	$PhCH_2$	H	H	H
238.	H	HN	O	4-OH-Ph	Me	$PhCH_2$	H	H	H
239.	H	HN	O	4-OH-Ph	Bn	$PhCH_2$	H	H	H
240.	H	HN	O	Ph	H	$HOCH_2$	H	H	H
241.	H	HN	O	Ph	Me	$HOCH_2$	H	H	H
242.	H	HN	O	Ph	Bn	$HOCH_2$	H	H	H
243.	H	HN	O	4-OH-Ph	H	$HOCH_2$	H	H	H
244.	H	HN	O	4-OH-Ph	Me	$HOCH_2$	H	H	H
245.	H	HN	O	4-OH-Ph	Bn	$HOCH_2$	H	H	H
246.	H	HN	O	Ph	H	$Bn(HOH_2C)CH$	H	H	H
247.	H	HN	O	Ph	Me	$Bn(HOH_2C)CH$	H	H	H
248.	H	HN	O	Ph	Bn	$Bn(HOH_2C)CH$	H	H	H
249.	H	HN	O	4-OH-Ph	H	$Bn(HOH_2C)CH$	H	H	H
250.	H	HN	O	4-OH-Ph	Me	$Bn(HOH_2C)CH$	H	H	H
251.	H	HN	S	Ph	H	$PhCH_2$	H	H	H
252.	H	HN	S	Ph	H	4-MeO-$PhCH_2$	H	H	H
253.	H	HN	S	Ph	Me	$PhCH_2$	H	H	H
254.	H	HN	S	Ph	Bn	$PhCH_2$	H	H	H
255.	H	HN	S	4-OH-Ph	H	$PhCH_2$	H	H	H
256.	H	HN	S	4-OH-Ph	Me	$PhCH_2$	H	H	H
257.	H	HN	S	4-OH-Ph	Bn	$PhCH_2$	H	H	H
258.	H	HN	S	Ph	H	$HOCH_2$	H	H	H
259.	H	HN	S	Ph	Me	$HOCH_2$	H	H	H
260.	H	HN	S	Ph	Bn	$HOCH_2$	H	H	H
261.	H	HN	S	4-OH-Ph	H	$HOCH_2$	H	H	H
262.	H	HN	S	4-OH-Ph	Me	$HOCH_2$	H	H	H
263.	H	HN	S	4-OH-Ph	Bn	$HOCH_2$	H	H	H
264.	H	HN	S	Ph	H	$Bn(HOH_2C)CH$	H	H	H
265.	H	HN	S	Ph	Me	$Bn(HOH_2C)CH$	H	H	H
266.	H	HN	S	Ph	Bn	$Bn(HOH_2C)CH$	H	H	H
267.	H	HN	S	4-OH-Ph	H	$Bn(HOH_2C)CH$	H	H	H
268.	H	HN	S	4-OH-Ph	Me	$Bn(HOH_2C)CH$	H	H	H

6. Process for the preparation of compounds of formula (I) according to Claim 1 wherein a compound of formula (II)



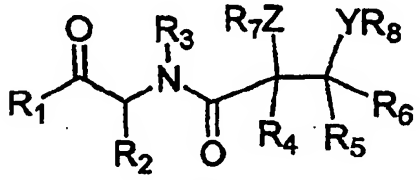
II

wherein R_1, R_2, R_3, are as above defined
is reacted with a compound of formula (III)



(III)

wherein R_4, R_5, R_6, Y and Z are as above defined and R_7 R_8 represent H or suitable protecting groups, (Pg) which can be same or different, cyclic or acyclic, and which can be cleaved in acidic conditions, in order to give a compound of formula (IV)



(IV)

wherein the substituents have the meaning as above, which is cyclised to a compound of formula (I) by action of an acid.

7. Process according to Claim 5 wherein the first step is performed in an aprotic polar solvent at a temperature comprised between 0 - 100°C for 1 - 24 hours.

8. Process according to Claim 6 wherein the reaction is performed in the presence of a coupling agent.

9. Process according to Claim 5 wherein the second step is performed in the presence of a strong acid at a temperature of 0°-150°C for 15min - 24 hours

10. Process according to Claim 8 wherein the acid is chosen in the group consisting of: sulphuric acid adsorbed on silica gel, p-toluen sulphonic acid, trifluoroacetic acid, trifluorometansulphonic acid.

11. Libraries consisting of compounds of formula (I) according to Claim 1.

12. Generation of combinatorial libraries according to Claim 10 in mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or automated fashion.

13. Use of compounds of formula 1 for the preparation of new leads for therapeutical applications.

14. Use of libraries consisting of compounds of formula 1 for the preparation of new leads for therapeutical applications.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 10 4135

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	13 July 2000	Herz, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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